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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/576,047 | HAMADA ET AL. | |
| | Examiner | Art Unit | |
| | KEVIN K. HILL | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *22 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *2,4-9,11-19,21,24 and 25* is/are pending in the application.

4a) Of the above claim(s) *7-9,13,14 and 17-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4-6,11,12,15,16,21,24 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

# Detailed Action

## *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 22, 2008 has been entered.

## *Election/Restrictions*

Applicant has elected the following species without traverse, wherein:
i) the virus is adenovirus, as recited in claim 2;
ii) the carrier cell is A549, as recited in claims 4 and 21;
iii) the promoter is 1A1.3B, as recited in claim 5;
iv) the therapeutic compound is atelocollagen, as recited in claim 6 and 16;
v) the viral administration rate of the virus for immunological treatment is set between about $10^5$ viral particles and $10^{11}$ viral particles for a patient with antibody negative to the virus, as recited in claim 12.

Because Applicant did not distinctly and specifically point out the supposed errors in the Group or species restriction requirement, the election has been treated as an election without traverse and the restriction and election requirement is deemed proper and therefore made final (MPEP § 818).

## *Amendments*

Applicant's response and amendments, filed December 22, 2008, to the prior Office Action is acknowledged. Applicant has cancelled Claims 1, 3, 10, 20 and 22-23, withdrawn Claims 7-9, 13-14 and 17-19, and amended Claims 12 and 24-25.

Claims 7-9, 13-14 and 17-19 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 2, 4-6, 11-12, 15-16, 21 and 24-25 are under consideration.

## *Priority*

This application is a 371 of PCT/JP04/15220, filed October 15, 2003. A certified copy of PCT/JP04/15220, filed October 15, 2003, is filed with the instant application. Accordingly, the effective priority date of the instant application is granted as October 15, 2003.

Acknowledgment is made of Applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) of JP 2003-354983, filed October 15, 2003.

However, it is noted that, the application PCT/JP04/15220, filed October 15, 2003 is in Japanese. Therefore, without a certified translation of PCT/JP04/15220, filed October 15, 2003, the effective filing date for the instant claims is the filing date of the instant application, April 14, 2006.

## *Examiner's Note*

Unless otherwise indicated, previous objections/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the December 22, 2008 response will be addressed to the extent that they apply to current rejection(s).

## *Claim Objections*

1. **The prior objections to Claims 3-4 and 21-25 are withdrawn** in light of Applicant's amendments to the claims to place the adjective "non-proliferative" closer to its noun "virus", and cancellation of duplicate claims.

## *Claim Rejections - 35 USC § 102*

2. **The prior rejection of Claims 2-3, 11-12, 15, 20 and 24-25 under 35 U.S.C. 102(e)** as being anticipated by Terman (2002/0177551 A1) **is withdrawn** in light of Applicant's argument that Terman does not disclose the method to comprise the following steps in the following order, as is required by the claims, wherein the steps are:

i) administer a carrier cell,

ii) administer a non-proliferative virus for immunological treatment to induce a CTL reaction,

iii) waiting a period after administering the virus before continuing with the cancer gene therapy method,

iii) after waiting the period of step (iii), growing a carrier cell with an oncolytic virus to produce an oncolytic virus infected carrier cell, wherein the oncolytic virus is the same type of virus as the virus for immunological treatment in step (ii) above, and
iv) administer the oncolytic virus-infected carrier cell, wherein the oncolytic virus is proliferative in the tumor cell.

Nor does Terman '551 disclose a kit or container that includes all three items [a non-proliferative virus for immunological treatment, a carrier cell, and the oncolytic virus] needed to practice the method in Claim 25.

The Examiner finds this argument persuasive.

## *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. **The prior rejection of Claims 2-4, 11-12, 15 and 20-25 under 35 U.S.C. 103(a)** as being unpatentable over Terman (2002/0177551 A1) and Harrison et al (Human Gene Therapy 12(10): 1323-1332, 2001) **is withdrawn** in light of Applicant's arguments regarding the teachings of Terman, discussed above.

4. **The prior rejection of Claims 6 and 16 under 35 U.S.C. 103(a)** as being unpatentable over Terman (2002/0177551 A1) and Harrison et al (Human Gene Therapy 12(10): 1323-1332, 2001), as applied to claims 2-4, 11-12, 15 and 20-25 above, and in further view of Ochiya et al

(Curr. Gene Therapy 1: 31-52, 2001) **is withdrawn** in light of Applicant's arguments regarding the teachings of Terman, discussed above.

5. **The prior rejection of Claim 5 stands rejected under 35 U.S.C. 103(a)** as being unpatentable over Terman (2002/0177551 A1), Harrison et al (Human Gene Therapy 12(10): 1323-1332, 2001) and Ochiya et al (Curr. Gene Therapy 1: 31-52, 2001), as applied to claims 2-4, 6, 11-12, 15-16 and 20-25 above, and in further view of Alemany et al (U.S. Patent 6,403,370 B1) and Barker et al (Genomics 38:215-222, 1996) **is withdrawn** in light of Applicant's arguments regarding the teachings of Terman, discussed above.

6. **Claims 11-12 and 25 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Lambright et al (Ann. Thorac. Surg. 68:1756-1762, 1999; *of record in IDS) in view of Morrison et al (J. Virol. 68(2):689-696, 1994) and Kirn et al (Nature Medicine 7(7):781-787, 2001).

The method comprises the following steps in the following order, as is required by the claims, wherein the steps are:

i) administer a carrier cell,

ii) administer a non-proliferative virus for immunological treatment to induce a CTL reaction,

iii) waiting a period after administering the virus before continuing with the cancer gene therapy method,

iii) after waiting the period of step (iii), growing a carrier cell with an oncolytic virus to produce an oncolytic virus infected carrier cell, wherein the oncolytic virus is the same type of virus as the virus for immunological treatment in step (ii) above, and

iv) administer the oncolytic virus-infected carrier cell, wherein the oncolytic virus is proliferative in the tumor cell.

***Determining the scope and contents of the prior art.***

Lambright et al teach a method of cancer gene therapy, the method comprising the step of administering a first carrier cell type, i.e. LLC cells, followed by the step of waiting a period of time, i.e. 3 days, followed by the step of growing a carrier cell with an oncolytic virus, i.e. HSV retrovirus, to produce an oncolytic virus infected carrier cell, followed by the step of

administering carrier cells infected with an oncolytic virus, wherein the oncolytic virus is proliferative in the tumor cell (step d) (pg 1758, col. 1, ¶1). The oncolytic virus would not only lyse tumor cells efficiently, but also induce a specific anti-tumor response in the host (pg 1759, col. 2, ¶2).

Lambright et al do not teach the step of administering a non-proliferative virus for immunological treatment after the step of administering the carrier cell and prior to the step of waiting a period before continuing with the method of cancer gene therapy. However, at the time of the invention, Morrison et al taught the immunization of a subject using a non-proliferative (pg 690, col. 1, lines 1-3) virus, the same type as the oncolytic virus, i.e. HSV-1 (pg 690, col. 1, Viruses), wherein the non-proliferative virus successfully elicited HSV-specific T cell-mediated immune responses (pg 693) and production of neutralizing antibodies (pg 691, col. 1, Assay of Antibody; pg 693, col. 2, Table 4). Morrison et al taught that the subject was immunized with $10^6$ virus particles (pg 690, col. 2, Inoculations), and the immune response is measurable by 4 weeks after challenge (pg 691).

***Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.***

People of the ordinary skill in the art will be highly educated individuals such as doctors, scientists, or engineers, possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in virology, oncology and immunology. Therefore, the level of ordinary skill in this art is high.

With respect to the limitation "for immunological treatment…to induce a cytotoxic T lymphocyte (CTL) reaction", those of ordinary skill in the art recognize that the CTL reaction induced in a host/subject/patient naturally flows in response to exposure to non-proliferative virus.

With respect to the limitation of step (c), after waiting the period [after administering the virus for immunological treatment and before continuing with the method of cancer gene therapy], growing a carrier cell with an oncolytic virus to produce an oncolytic virus infected

carrier cell, Lambright et al teach that the carrier cell was infected with the oncolytic virus four hours before injection into the host/subject/patient (pg 1758, col. 1, ¶1). Thus, it would be both common sense and logically flow that one of ordinary skill in the art would wait a period of time after administering a non-proliferative virus for immunological treatment to ascertain the immune response to the non-proliferative virus for immunological treatment before continuing with the method of cancer gene therapy, i.e. freshly producing carrier cells infected with the oncolytic virus shortly before injection into the host/subject/patient.

***Considering objective evidence present in the application indicating obviousness or nonobviousness.***

It would have been obvious to one of ordinary skill in the art to combine the step of administering a non-proliferative virus for immunological treatment to a patient to induce a CTL reaction within the patient after administering a carrier cell and waiting a period before continuing with the method of cancer gene therapy comprising administering carrier cells infected with an oncolytic virus the same type as the non-proliferative virus for immunological treatment with a reasonable chance of success because all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. An artisan would be motivated to combine the step of administering a non-proliferative virus for immunological treatment to a patient to induce a CTL reaction within the patient after administering a carrier cell and waiting a period before continuing with the method of cancer gene therapy comprising administering carrier cells infected with an oncolytic virus the same type as the non-proliferative virus for immunological treatment because at the time of the instant asserted invention, those of ordinary skill in the art recognized that the immune response of the host/subject/patient will likely limit on-going viral replication and spread in immunocompetent patients eventually, although immune responses may also lead to enhanced anti-tumor effects (Kirn et al, pg 785, col. 2, ¶2). Important factors for the development of virotherapy include the parental virus strain and the level of pre-existing immunity to the parental virus in the population. The lack of an immunocompetent model for oncolytic viruses has been a critical limitation, and hurdles such as

immune response are a major potential limitation that must be addressed in the development of a virotherapy platform for the treatment of cancer (pg 786, col. 1). A balance between efficient viral replication and induction of the host immune response will be essential for this therapy to be effective (Lambright et al, pg 1760, col. 1). Thus, the steps of administering a non-proliferative virus for immunological treatment to a patient to induce a CTL reaction within the patient after administering a carrier cell and waiting a period before continuing with the method of cancer gene therapy comprising administering carrier cells infected with an oncolytic virus the same type as the non-proliferative virus for immunological treatment will more closely model the real-world situation of patients with pre-existing immunity to the oncolytic virus used for therapeutic treatment, an art-recognized problem that must be addressed in the development of a virotherapy platform for the treatment of cancer.

Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

7. **Claim 15 is rejected under 35 U.S.C. 103(a)** as being unpatentable over Lambright et al (Ann. Thorac. Surg. 68:1756-1762, 1999; *of record in IDS) in view of Morrison et al (J. Virol. 68(2):689-696, 1994) and Kirn et al (Nature Medicine 7(7):781-787, 2001), as applied to Claims 11-12 and 25 above, and in further view of Terman (2002/0177551 A1; *of record).

***Determining the scope and contents of the prior art.***

Neither Lambright et al, Morrison et al nor Kirn et al teach wherein the administration of the oncolytic virus infected carrier cell is by intratumor injection. However, at the time of the invention, Terman disclosed a method of treating tumors comprising a step of administering to a patient *in vivo* with $10^{10}$ virus particles (pg 159, [2067]) comprising a nucleic acid viral vector to induce a CTL reaction, and after a predetermined period of time, e.g., at least three weeks (pg 94, Table V), the method further comprising a step of administering to said patient carrier cells infected with an oncolytic virus (pg 54, [0544, 0549]; pg 90-91, [1057-1058, 1060, Example V]), wherein said carrier cell may be a tumor cell (pg 8, [0052]), wherein the carrier cell infected with an oncolytic virus is administered to the patient into the host tumor (pg 90, [1056]).

***Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.***

People of the ordinary skill in the art will be highly educated individuals such as doctors, scientists, or engineers, possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in virology, oncology and immunology. Therefore, the level of ordinary skill in this art is high.

***Considering objective evidence present in the application indicating obviousness or nonobviousness.***

It would have been obvious to one of ordinary skill in the art to try administering the oncolytic virus infected carrier cell by intratumoral injection in a cancer gene therapy method of Lambright et al in view of Morrison et al because "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipate success, it is likely that product not of innovation but of ordinary skill and common sense." The ordinary artisan recognizes that the oncolytic virus infected carrier cell may be placed into, adjacent to, near or far from the tumor for treatment, and thus there are but four design options immediately envisaged by the routineer. An artisan would be motivated to try administering the oncolytic virus infected carrier cell by intratumoral injection in a cancer gene therapy method because such direct placement of the oncolytic virus infected carrier cell would allow the oncolytic virus to infect the tumor cells to be treated with minimal or no exposure to neutralizing antibodies, and thereby improve the likelihood of killing the undesired tumor cells.

Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

8. **Claim 16 is rejected under 35 U.S.C. 103(a)** as being unpatentable over Lambright et al (Ann. Thorac. Surg. 68:1756-1762, 1999; *of record in IDS) in view of Morrison et al (J. Virol. 68(2):689-696, 1994) and Kirn et al (Nature Medicine 7(7):781-787, 2001), as applied to Claims 11-12 and 25 above, and in further view of Ochiya et al (Curr. Gene Therapy 1: 31-52, 2001; *of record).

***Determining the scope and contents of the prior art.***

Neither Lambright et al, Morrison et al nor Kirn et al teach wherein the administration of the oncolytic virus infected carrier cell with atellocollagen. However, at the time of the

invention, Ochiya et al reviewed the advantages of using atelocollagen to mediate controlled-release of bioactive agents of molecular medicines (pg 33, Figure 1).

***Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.***

People of the ordinary skill in the art will be highly educated individuals such as doctors, scientists, or engineers, possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in virology, oncology and immunology. Therefore, the level of ordinary skill in this art is high.

***Considering objective evidence present in the application indicating obviousness or nonobviousness.***

It would have been obvious to one of ordinary skill in the art to combine atellocollagen with the carrier cell infected with the oncolytic virus in a method of cancer gene therapy with a reasonable chance of success because all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. An artisan would be motivated to combine atellocollagen with the carrier cell infected with the oncolytic virus in a method of cancer gene therapy because Ochiya et al teach that atelocollagen may be designed to degrade *in vivo* or be surgically removed (pg 38, Figure 5), is useful for the prolonged release of viral vectors *in vivo* (pgs 40-41), and may be used as a carrier for cell-based therapies (pgs 46-47, Figure 12).

Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

9. **Claims 2 and 24 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Lambright et al (Ann. Thorac. Surg. 68:1756-1762, 1999; *of record in IDS) in view of Morrison et al (J. Virol. 68(2):689-696, 1994) and Kirn et al (Nature Medicine 7(7):781-787, 2001), as

applied to Claims 11-12 and 25 above, and in further view of Molnar-Kimber et al (WO 99/45783; September 16, 1999;* of record in IDS) and Inglis et al (U.S. Patent 5,837,261).

***Determining the scope and contents of the prior art.***

Neither Lambright et al, Morrison et al nor Kirn et al teach a kit comprising the non-proliferative virus for immunological treatment, the carrier cell to be infected with the oncolytic virus, and the oncolytic virus. However, at the time of the invention, Molnar-Kimber et al disclosed pharmaceutical compositions for killing tumor cells in a subject, the composition comprising a carrier cell that is to be infected with an oncolytic virus, wherein one or more components of the pharmaceutical composition may be packaged in a kit comprising the producer [carrier] cells (Abstract; pgs 22-23, joining ¶). The oncolytic virus may incapable of replicating in any cell of the subject [non-replicative], or may be incapable of replicating in a non-tumor cell of the subject (pg 6, lines 25-29), and may be a HSV-1 virus or an adenovirus (pg 7, lines 6-7).

Neither Lambright et al, Morrison et al, Kirn et al nor Molnar-Kimber et al teach the kit may comprise an inactivated virus for immunological treatment. However, at the time of the invention, Inglis et al disclosed containers [kits] comprising inactivated virus, i.e. HSV, for immunological treatment, i.e. vaccination (e.g. claims 1 and 16).

***Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.***

People of the ordinary skill in the art will be highly educated individuals such as doctors, scientists, or engineers, possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in virology, oncology and immunology. Therefore, the level of ordinary skill in this art is high.

***Considering objective evidence present in the application indicating obviousness or nonobviousness.***

It would have been obvious to one of ordinary skill in the art to package the non-proliferative virus for immunological treatment, the carrier cell to be infected with the oncolytic virus, and the oncolytic virus in a kit with a reasonable chance of success because one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. At the time of the instantly asserted invention, those of ordinary skill in the art were well-aware that each component of a therapeutic composition may be packaged into a kit. An artisan would be motivated to package the non-proliferative virus for immunological treatment, the carrier cell to be infected with the oncolytic virus, and the oncolytic virus in a kit because such would provide all the ingredients of a therapeutic composition into one container, and thus easily accessible by the routineer.

Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

10. **Claims 4 and 21 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Lambright et al (Ann. Thorac. Surg. 68:1756-1762, 1999; *of record in IDS) in view of Morrison et al (J. Virol. 68(2):689-696, 1994), Kirn et al (Nature Medicine 7(7):781-787, 2001), Molnar-Kimber et al (WO 99/45783; September 16, 1999;* of record in IDS) and Inglis et al (U.S. Patent 5,837,261), as applied to Claims 2, 11-12 and 24-25 above, and in further view of Harrison et al (Human Gene Therapy 12(10): 1323-1332, 2001; *of record).

***Determining the scope and contents of the prior art.***

Neither Lambright et al, Morrison et al, Kirn et al, Molnar-Kimber et al nor Inglis et al teach the carrier cells are A549 cells. However, at the time of the invention, Harrison et al taught the use of A549 cells to produce oncolytic adenoviruses in a method to treat tumors.

***Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.***

People of the ordinary skill in the art will be highly educated individuals such as doctors, scientists, or engineers, possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the

practical experience in virology, oncology and immunology. Therefore, the level of ordinary skill in this art is high.

At the time of the invention, those of ordinary skill in the art recognized reasonable predictability that carrier cells infected with oncolytic viruses *in vitro* perform the same function as when administered to a host/subject/patient *in vivo*. For example, Lambright et al teach that the oncolytic virus replicates in the carrier cells *in vitro* (pg 1758) and that carrier cells serve as a means of viral delivery *in vivo* (pg 1759, col. 2). Similarly, Harrison teach that their *in vivo* results are an extension of their *in vitro* experiments regarding the ability of A549 carrier cells to support replication of an oncolytic virus (pg 1330, col. 1, ¶1).

***Considering objective evidence present in the application indicating obviousness or nonobviousness.***

It would have been obvious to one of ordinary skill in the art to substitute a first carrier cell type as taught by Lambright et al with a second carrier cell type, i.e. A549 cells, as taught by Harrison et al with a reasonable chance of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945). When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. In the instant case, both LLC and A549 cells are recognized in the prior art as carrier cells for oncolytic viruses, and thus each performs the same function for the same purpose. An artisan would be motivated to substitute a first carrier cell type with a second carrier cell type, i.e. A549 cells, because each oncolytic virus has a cellular tropism, and depending on the type of oncolytic virus being used and the type of tumor that is to be treated, the artisan would know which carrier cell type would be consistent with the oncolytic virus tropism. Thus, selection of the carrier cell type is but a design choice for the artisan that reflects the oncolytic virus to be used in the cancer gene therapy method.

Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

11. **Claim 5 is rejected under 35 U.S.C. 103(a)** as being unpatentable over Lambright et al (Ann. Thorac. Surg. 68:1756-1762, 1999; *of record in IDS) in view of Morrison et al (J. Virol. 68(2):689-696, 1994), Kirn et al (Nature Medicine 7(7):781-787, 2001), Molnar-Kimber et al (WO 99/45783; September 16, 1999;* of record in IDS), Inglis et al (U.S. Patent 5,837,261) and Harrison et al (Human Gene Therapy 12(10): 1323-1332, 2001; *of record) as applied to Claims 2, 4, 11-12, 21 and 24-25 above, and in further view of Alemany et al (U.S. Patent 6,403,370 B1; *of record) and Hamada et al (Cancer Res. 63:2506-2512, 2003; *of record in IDS).

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers, PCT/JP04/15220 or JP 2003-354983, has not been made of record in accordance with 37 CFR 1.55. See MPEP §201.15.

***Determining the scope and contents of the prior art.***

Neither Lambright et al, Morrison et al, Kirn et al, Molnar-Kimber et al, Inglis et al nor Harrison et al teach the oncolytic virus to comprise a 1A1.3B promoter. However, at the time of the invention, Alemany et al disclosed a method for killing tumor target cells, the method comprising an oncolytic adenoviral vector, wherein the oncolytic adenoviral vector comprises a tumor cell-activated promoter operably linked to the adenoviral E1 gene (col. 6, lines 24-37).

Alemany et al do not disclose the use of a tumor cell-activated promoter 1A1.3B. However, at the time of the invention, Hamada et al taught the use of a tumor cell-activated 1A1.3B promoter in the context of an oncolytic virus for ovarian cancer gene therapy.

***Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.***

People of the ordinary skill in the art will be highly educated individuals such as doctors, scientists, or engineers, possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in virology, oncology, immunology and molecular biology. Therefore, the level of ordinary skill in this art is high.

***Considering objective evidence present in the application indicating obviousness or nonobviousness.***

It would have been obvious to one of ordinary skill in the art to substitute a tumor cell-activated promoter as taught by Alemany for a 1A1.3B promoter as taught by Hamada et al in an oncolytic virus with a reasonable chance of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945). When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. In the instant case, the prior art recognized that products of the adenovirus E1 gene control the replication of the adenovirus vector in tumor cells, and thus the use of a tumor cell-activated promoter to regulate the expression of E1 gene products would confer or enhance specificity of viral replication in the tumor cells. The art also recognized the existence of many tumor-activated promoters, including 1A1.3B, wherein the 1A1.3B gene product is an art-recognized ovarian cancer marker antigen. Hamada et al successfully demonstrate ovarian cancer-specific 1A1.3B promoter activity and suggest the usefulness of the 1A1.3B promoter for the generation of ovarian cancer-specific oncolytic viral vectors for the development of cancer-specific oncolytic viral therapies.

Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

12. **Claim 6 is rejected under 35 U.S.C. 103(a)** as being unpatentable over Lambright et al (Ann. Thorac. Surg. 68:1756-1762, 1999; *of record in IDS) in view of Morrison et al (J. Virol. 68(2):689-696, 1994), Kirn et al (Nature Medicine 7(7):781-787, 2001), Molnar-Kimber et al (WO 99/45783; September 16, 1999;* of record in IDS), Inglis et al (U.S. Patent 5,837,261), Harrison et al (Human Gene Therapy 12(10): 1323-1332, 2001; *of record), Alemany et al (U.S. Patent 6,403,370 B1; *of record) and Hamada et al (Cancer Res. 63:2506-2512, 2003; *of record

in IDS). as applied to Claims 2, 4-5, 11-12, 21 and 24-25 above, and in further view of Ochiya et al (Curr. Gene Therapy 1: 31-52, 2001; *of record).

***Determining the scope and contents of the prior art.***

Neither Lambright et al, Morrison et al, Kirn et al, Molnar-Kimber et al, Inglis et al, Harrison et al, Alemany et al nor Hamada et al teach the kit to comprise atelocollagen. However, at the time of the invention, Ochiya et al reviewed the advantages of using atelocollagen to mediate controlled-release of bioactive agents of molecular medicines (pg 33, Figure 1).

***Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.***

People of the ordinary skill in the art will be highly educated individuals such as doctors, scientists, or engineers, possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in virology, oncology and immunology. Therefore, the level of ordinary skill in this art is high.

***Considering objective evidence present in the application indicating obviousness or nonobviousness.***

It would have been obvious to one of ordinary skill in the art to combine atellocollagen with the kit comprising the non-proliferative virus for immunological treatment, the carrier cell to be infected with the oncolytic virus, and the oncolytic virus with a reasonable chance of success because all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. An artisan would be motivated to combine atellocollagen with the kit comprising the non-proliferative virus for immunological treatment, the carrier cell to be infected with the oncolytic virus, and the oncolytic virus because Ochiya et al teach that atelocollagen may be designed to degrade *in vivo* or be surgically removed (pg 38, Figure 5), is useful for the prolonged release of viral vectors *in vivo* (pgs 40-41), and may be used as a carrier for cell-based therapies (pgs 46-47, Figure 12).

Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

## *Double Patenting*

13. **The prior provisional rejection of Claims 2-6 and 20-24 on the ground of nonstatutory obviousness-type double patenting** as being unpatentable over claims 1-5 of copending Application No. 10/575,894 **is withdrawn** in light of Applicant's filing of a Terminal Dislcaimer, which has been approved (paper entry dated January 28, 2009).

## *Conclusion*

14. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to KEVIN K. HILL whose telephone number is (571)272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill/

Examiner, Art Unit 1633